REMARKS

Claims 1-40 are pending and have been rejected in the above-identified application. Applicants have amended claim 1 for the sake of clarification and to correct for inadvertent typographical errors. Support for all amendments are found in the originally filed specification. No new matter has been added to the claims or specification by amendment.

Attached herewith is a Supplemental Information Disclosure Statement Under 37 C.F.R. § 1.97(c).

Applicants request consideration and entry into the record of the following amendments and remarks.

Rejection Under 35 U.S.C. §102(a)

Claims 35-40 are rejected under 35 U.S.C. §102(b) as being anticipated by U.S Pat. No. 4,503,067 to Wiedemann et al. ("Wiedemann"; Filed: April 4, 1983; Issued: March 5, 1985).

The Examiner states that Wiedemann discloses carbazolyl-(4)-oxypropanolamine compounds, corresponding pharmaceutical compositions and treatment methods for circulatory and cardiac diseases (such as hypertension, angina pectoris).

The Examiner maintains that Wiedemann anticipates the claimed invention as it discloses a pharmaceutical composition containing carvedilol (in Ex. 2 and claim 8) and a method of treating hypertension and angina pectoris. The Examiner also states that "[the] instant hydrate and anhydrous forms are not maintained in pharmaceutical compositions as well as following in vivo administration".

Applicants respectfully traverse the rejection for the following reasons.

In general, the present invention relates to a hydrobromide salt, anhydrate or solvate form of carvedilol, corresponding compositions containing or treatment methods using carvedilol hydrobromide form(s) for specific disease states in mammals. Specifically, the present invention relates to a novel form of carvedilol hydrobromide, which is the hydrobromide salt of 1-(carbazol-4-yloxy-3-[[2-(o-methoxy-phenoxy)ethyl]amino]-2-propanol, and/or other carvedilol solvates thereof, corresponding compositions containing and methods of using the aforementioned compound(s) to treat hypertension, congestive heart failure, and angina, etc.

Particular compounds disclosed in the present invention, include, but are not limited to carvedilol hydrobromide monohydrate, carvedilol hydrobromide dioxane solvate, carvedilol hydrobromide 1-pentanol solvate, carvedilol hydrobromide 2-methyl-1-propanol solvate, carvedilol hydrobromide trifluoroethanol solvate, carvedilol hydrobromide 2-propanol solvate, carvedilol hydrobromide n-propanol solvate #1, carvedilol hydrobromide n-propanol solvate

#2, carvedilol hydrobromide ethanol solvate, or carvedilol hydrobromide anhydrous.

Claims 35 to 40 of the present invention generally are directed to pharmaceutical compositions containing carvedilol hydrobromide salt, solvate or anhydrate derivatives and respective treatment methods using the aforementioned derivatives or compositions. Claim 35 discloses a pharmaceutical composition comprised of a compound of claim 1 (i.e., identified as carvedilol hydrobromide monohydrate) and claim 36 discloses a pharmaceutical composition of a compound of claim 30 (i.e., identified as carvedilol hydrobromide anhydrous). Claims 37 to 40 disclose treatment methods for hypertension, congestive heart failure or angina comprised of administering a compound of claim 1 or claim 30, or corresponding pharmaceutical compositions thereof.

In light of the foregoing, the present invention is not anticipated by Wiedemann, which neither teaches a pharmaceutical composition, nor suggests treatment methods containing or using carvedilol hydrobromide salts, anhydrates or solvates of the present invention.

Wiedemann provides no disclosure as to how to obtain or make any one of the compound derivatives or pharmaceutical compositions containing those derivatives of the present invention.

Wiedemann teaches and claims the free base form of carvedilol (i.e., 1-[carbazolyl-(4)-oxy]-3-[2-(2-methoxyphyenoxy)-ethylamino]-propan-2-ol; see Example 2 and claim 8 therein), but Wiedemann does not teach a carvedilol hydrobromide salt, anhydrate or solvate form thereof, corresponding pharmaceutical compositions or treatment methods using the aforementioned derivatives as taught in the present invention.

In light of the above, Wiedemann fails to teach each and element of the claimed invention, because Wiedemann does not disclose carvedilol hydrobromide salt, anhydrate or solvate form thereof, corresponding pharmaceutical compositions or treatment methods using the aforementioned derivatives as taught in the present invention.

Therefore, Wiedemann does not anticipate the claimed invention.

Moreover, applicants respectfully point out that the Examiner did not set forth a prima facie showing or basis for the statement set forth in the above-identified rejection that:

> "[the] instant hydrate and anhydrous forms are not maintained in pharmaceutical compositions as well as following in vivo administration".

In particular, as the Examiner did not indicate where the specific limitation is taught in Wiedemann or what constituted the Examiner's specific rationale, reasoning or scientific basis for the above-identified statement, the aforementioned statement merely is a conclusory statement without basis in fact.

Ordinarily, there must be some form of evidence in the record to support an assertion of common knowledge. See *Lee*, 277 F.3d at 1344-45, 61 USPQ2d at 1434-35 (Fed. Cir. 2002); *Zurko*, 258 F.3d at 1386, 59 USPQ2d at 1697 . . . If such notice is taken, the basis for such reasoning must be set forth explicitly. The examiner must provide specific factual findings predicated on sound technical and scientific reasoning to support his or her conclusion of common knowledge. See *Soli*, 317 F.2d at 946, 37 USPQ at 801; *Chevenard*, 139 F.2d at 713, 60 USPQ at 241. The applicant should be presented with the explicit basis on which the examiner regards the matter as subject to official notice and be allowed to challenge the assertion in the next reply after the Office action in which the common knowledge statement was made (see, M.P.E.P. Section 2144.03 (A), (B) and (C)).

M.P.E.P. Section 2144.03 (A), (B) and (C) states that:

> "It would not be appropriate for the examiner to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known. For example, **assertions of technical facts in the areas of esoteric technology or specific knowledge of the prior art must always be supported by citation to some reference work recognized as standard in the pertinent art.** *In re Ahlert*, 424 F.2d at 1091, 165 USPQ at 420-21. See also *In re Grose*, 592 F.2d 1161, 1167-68, 201 USPQ 57, 63 (CCPA 1979) ("[W]hen the PTO seeks to rely upon a chemical theory . . . it must provide evidentiary support for the existence and meaning of that theory.") . . .
>
> It is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record, as the principal evidence upon which a rejection was based. *Zurko*, 258 F.3d at 1385, 59 USPQ2d at 1697 **("[T]he Board cannot simply reach conclusions based on its own understanding or experience-or on its assessment of what would be basic knowledge or common sense. Rather, the Board must point to some concrete evidence in the record in support of these findings.")**. . ." *Id.* at 1385-86, 59 USPQ2d at 1697.
>
> As the court held in *Zurko*, **an assessment of basic knowledge and common sense that is not based on any evidence in the record lacks substantial evidence support**. *Id.* at 1385, 59 USPQ2d at 1697. See also *In re Lee*, 277 F.3d 1338, 1344-45, 61 USPQ2d 1430, 1434-35 (Fed. Cir. 2002) (In reversing the Board's decision, the court stated "'common knowledge and common sense' on which the Board relied in rejecting Lee's application are not the specialized knowledge and expertise contemplated by the Administrative Procedure Act. **Conclusory statements such as those here provided do not fulfill the agency's obligation..The board cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but must set forth the rationale on which it relies.")**. . ."

In light of the above, applicants request that the above rejection under 35 U.S.C. § 102(b) be withdrawn.

Rejection Under 35 U.S.C. §103(a)

Claims 1-40 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,699,997 to Hildesheim . ("Hildesheim"; Filed: June 28, 2001, Issued: March 2, 2004).

The Examiner states that while Hildesheim does not disclose preparing carvedilol hydrobromide hydrate and solvate forms of the present invention, it does disclose new crystalline hydrate and solvate forms of carvedilol, such as carvedilol hydrochloride hydrate and anhydrous forms, a process for preparing and pharmaceutical compositions containing such forms.

The Examiner also states it would have been obvious to one of skill in the art to be motivated to prepare the crystalline hydrate and solvate forms of carvedilol of the present invention as Hildesheim teaches that the existence and physical properties of different crystals can be determined by a variety of techniques (such as differential scanning calorimetry, X-ray diffraction and infrared spectroscopy), that carvedilol exhibits polymorphism, where polymorphic forms (e.g., hydrates and solvate) exhibit advantages as solubility in aqueous solution (gastric juices of patient), and that polymorphic forms easily are processed into pharmaceutical dosages.

Applicants respectfully traverse the above-identified rejection.

According to the M.P.E.P Section 2142, to establish a case of prima facie obviousness, three basic criteria must be met:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.
>
> Second, there must be a reasonable expectation of success.
>
> Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicants respectfully submit that Hildesheim fails to support a *prima facie* case of obviousness or to provide any motivation to try or to make the present invention for the following reasons.

Hildesheim teaches a process for preparing carvedilol and in particular a carvedilol hydrochloride hydrate form, defined as "a crystalline material having a water content of about or above 2% w/w (see col. 5, lines 13-15)".

In contrast, the carvedilol hydrobromide salt, solvate, anhydrate, polymorphic forms of the present invention are different from carvedilol hydrochloride polymorphic forms as taught by Hildesheim.

More importantly, Hildesheim provides only disclosure with regard to carvedilol hydrochloride, but provides no disclosure as to how to obtain any one or more of the carvedilol hydrobromide forms of the present invention.

The present invention teaches salt, anhydrate or solvate forms of carvedilol hydrobromide, corresponding compositions containing and treatment methods using the aforementioned forms for specific cardiovascular diseases. Compounds of the present invention, include, but are not limited to carvedilol hydrobromide monohydrate, carvedilol hydrobromide dioxane solvate, carvedilol hydrobromide 1-pentanol solvate, carvedilol hydrobromide 2-methyl-1-propanol solvate, carvedilol hydrobromide trifluoroethanol solvate, carvedilol hydrobromide 2-propanol solvate, carvedilol hydrobromide n-propanol solvate #1, carvedilol hydrobromide n-propanol solvate #2, carvedilol hydrobromide ethanol solvate, or carvedilol hydrobromide anhydrous.

While one of ordinary skill in the art would generally understand that "polymorphism is the property of some molecules and molecular complexes to assume more than one crystalline form in the solid state [and] that a single molecule may give rise to a variety of crystal forms (also called "polymorphs", "hydrates" or solvates") having distinct physical properties" as taught by Hildesheim (see col. 2, lines 50-60), the conventional chemical literature supports the novelty and unobviousness of polymorphic forms of the present invention by teaching that each polymorphic form has different physical and chemical differences and properties than other polymorphic form(s).

> For example, the chemical literature teaches that:
>
> "Different polymorphs of a given compound are in general as different in structure and properties as the crystals of two different compounds. Solubility, melting point, density, hardness, crystal shape, optical and electrical properties, vapour pressure, stability, etc. all vary with the polymorphic forms . . ."; and that
>
> even though two polymorphs of a given compound may have identical compositions (e.g., two hydrates containing the same amount of water), the form and properties of each of these polymorphs would, in general, be different (See generally, Chemical & Engineering News, February 24, 2003, pp. 32-35; and Jain et al., "Polymorphism in Pharmacy", Indian Drugs, 23 (6), 1986, pp. 315 -329).

Moreover, the fact that Hildesheim teaches that a variety of detection techniques, such as differential scanning calorimetry, X-ray diffraction and infrared spectroscopy, can determine the existence of or differentiate between different polymorphic forms only

indicates that conventional art known diagnostic identification tools are available to the skilled artisan to verify a specific compound, such as a polymorphic form, has been made.

However, even in light of the art, it would not be obvious how an ordinary artisan could determine which specific or different polymorphic forms of carvedilol to prepare by reaction with different acids, reagents or other solvents or varying other properties, parameters, etc., without further experimentation.

Applicants respectfully point out that obvious to try or experiment is not the standard under 35 U.S.C. § 103, where "the prior art gave no indication of which parameters were critical or no direction as to which of the possible choices is likely to be successful (see, MPEP Section 2145 (X)(B) at lines 6-12). There must be a motivation to pick, use, combine or prepare compounds with specific functional group components or conduct functional group conversions of compounds taught by the present invention by reaction with various known chemical reagents to generate derivative compounds which may be taught by another art reference. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some teaching, suggestion or incentive supporting the combination. *In re Geiger*, 2 USPQ 2d 1276 (Fed. Cir. 1987).

Absent such suggestions, there would be no reasonable reason why one skilled in the art would be motivated to prepare polymorphic forms of carvedilol hydrobromide taught by the present invention in view of Hildesheim without some teaching, suggestion or incentive supporting such a product as it is well known in the art, as even Hildesheim teaches that:

> "the existence and physical properties of polymorphs, hydrates and solvates is unpredictable (see Hildesheim, col. 3, lines 4-5)".

It is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F. 2d. 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges*, 783 F. 2d. 1038, 228 USPQ 685 (Fed. Cir. 1986).

Moreover, in view of the above, there would be no reasonable expectation of success that a carvedilol hydrobromide salt would exhibit the same chemical and physical properties of the carvedilol hydrochloride polymorphs, hydrates and solvates taught in Hildesheim, such as solubility in aqueous solution (gastric juices of patient). Further distinguished from Hildesheim, the present invention relates to a novel salt, anhydrate or solvate form of carvedilol hydrobromide "with greater aqueous solubility, chemical stability, etc. offering many potential benefits for provision of medicinal products containing the drug carvedilol, but further include the ability of polymorphs of the present invention to achieve desired or prolonged drug levels in a systemic system by sustaining absorption along the gastro-

intestinal tract of mammals (i.e., such as humans), particularly in regions of neutral pH, where a drug, such as carvedilol, has minimal solubility (see specification at page 2, lines 22-30)".

In view of the distinctions pointed out *supra*, Hildesheim does not teach or suggest the necessary elements which are critical or essential to form or produce the novel carvedilol hydrobromide forms of the present invention.

For the record, applicants note that the courts have addressed the patentability of polymorphs and have indicated that the demonstration of "unexpected results" is not required to establish the patentability of novel crystalline forms.

The federal courts have long held that new crystalline forms of old compounds are patentable and are not obvious over other forms of the old compound. *Bristol-Myers Co. v. U.S. International Trade Commission*, 15 USPQ 2d 1258 (Fed. Cir. 1989, unpublished), provides a review of decisions affirming the patentability of new crystal forms. See for example *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966), *In re Irani* 427 F.2d 806, 166 USPQ 24 (CCPA 1970), and *In re Grose,* 592 F.2d 116, 201 USPQ 57 (CCPA 1979).

The court in *Grose* specifically rejected the application of the law of structural obviousness, and hence a requirement for a showing of unobvious properties, when analyzing the patentability of novel crystalline forms. (M.P.E.P. 2144.02)

> No reason exists for applying the law relating to structural obviousness of those compounds which are homologs or isomers of each other to this case. When the PTO seeks to rely upon a chemical theory, in establishing a prima facie case of obviousness, it must provide evidentiary support for the existence and meaning of that theory. In re Mills, 47 CCPA 1185, 1191, 281 F.2d 218, 223-24, 126 USPQ 513, 517 (1960). The known structural relationship between adjacent homologs, for example, supplies a chemical theory upon which a prima facie case of obviousness of a compound may rest. A zeolite, like those of the instant case, is not a compound which is a homolog or isomer of another, but is a mixture of various compounds related to each other by a particular crystal structure. Moreover, no other chemical theory has been cited as a basis for considering appellants' zeolite as prima facie obvious in view of Milton's zeolite R.

In re Grose, 592 F.2d 1161,1167-1168, 201 USPQ 57,63 (CCPA 1979).

Based upon the foregoing, applicants respectfully maintain that a prima facie case of obviousness has not been made by Hildesheim.

In light of the above, applicants request that the above rejection under 35 U.S.C. §103(a) be withdrawn.

Double Patenting

Claims 1 to 40 are provisionally rejected under the judicially created doctrine of nonstatutory double patenting over claims 1-2, 33-34 and 41-42 of co-pending U.S. Patent Appln. Ser. No. 10/997,230. The Examiner has indicated that this is a provisional double patenting rejection since the conflicting claims of the aforementioned co-pending application while not identical are not patentably distinct from each other.

Applicants request that the above-identified rejection be held in abeyance until the determination of patentable subject matter of the present invention.

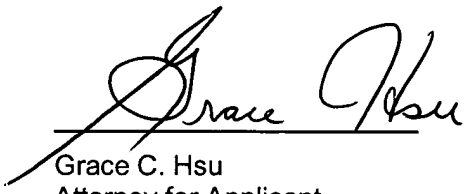
CONCLUSION

In view of the above amendments and remarks, reconsideration of this application is requested. Applicants believe that the claims of the present application are in condition for allowance and is earnestly solicited. Applicants respectfully request that a timely Notice of Allowance be issued in the present application.

If any additional fees or charges are required authorization is hereby granted to charge any necessary fees to Deposit Account No. 19-2570 accordingly.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned attorney at the number below.

Respectfully submitted,



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